

# SYMPOSIUM ON WORLD MEDICINE

## The Future of Immunization

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EVER SINCE Jenner established the principle of vaccination more than a century and a half ago, immunization has been the most efficient method ever devised for protecting men and animals from disease. Under ideal conditions, it converts a susceptible man to a resistant man, enabling him to move wherever he chooses, whenever he chooses, carrying his protection with him. Unlike chemoprophylaxis, immunization frees him from having to take a drug regularly, with the risk of running out of the supply of the drug or the mental hazard of forgetting to use it. Unlike water sanitation or insect control, immunization permits him to leave a protected area without leaving his protection behind him. And no longer must he periodically flee an epidemic area, hoping that he has left in time.

Gains such as these, unparalleled in preventive medicine, have saved millions of lives and freed other millions from panic or from chronic fear. But few immunizing procedures approach this ideal. Even smallpox vaccination does not provide lifetime protection (as Jenner first thought), and most other immunizing procedures, with the probable exception of yellow fever vaccination, appear to be limited in the duration of their efficacy. More serious is the imperfect degree of protection afforded by the majority of vaccines. In addition to smallpox and yellow fever vaccines, only one other virus vaccine is strikingly effective, poliovirus vaccine.

We have an excellent bacterial vaccine against whooping cough, a relatively good one against

tuberculosis, and a moderately effective one against typhoid fever; remarkably effective toxoids against diphtheria and tetanus; highly effective but now obsolete polysaccharide antigens against pneumococcus infections; vaccines against typhus fever and Rocky Mountain spotted fever, both considered very useful but not in the same class as yellow fever vaccine; and moderately good virus vaccines against influenza and rabies. Aside from certain specialized vaccines such as those for tularemia, brucellosis, and adult adenovirus infections, and those now under development like measles vaccine, this list is virtually complete except for a series of preparations the usefulness of which is hard to establish: vaccines against cholera, plague, mumps, paratyphoid fever, staphylococcus infections, and the like.

When one considers the well-known limitations of these agents and the list of infectious diseases for which no really useful vaccination procedure is available, the record is far from satisfactory, and it is difficult to agree with the statement recently credited to Sir Macfarlane Burnet (1) that "today the technique of immunization provides protection against all the significant diseases that have not been eliminated by public health measures or that do not yield readily to chemotherapy." The fact is that there are still great deficiencies in our knowledge of both the principles and the application of immunization. Nevertheless, there are many good reasons to believe that major progress can be achieved to remedy these deficiencies in the future.

But one may ask, Is this the major path to follow? With the tremendous, continuing advances in antibiotic therapy, with the prospect of steadily increasing sanitation extending throughout the world, and in view of the diffi-

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culties that have beset past efforts to immunize against many infectious diseases, is a major effort to continue the extended application of immunology to control infectious diseases justified? Or should one take the position that the easy problems in immunization have been solved, and that the difficult ones will either be insoluble or will be solved more readily by other approaches?

Let us first consider immunization as we see it today. Surely little doubt exists of the lasting usefulness of smallpox vaccine, pertussis vaccine, diphtheria and tetanus toxoids, yellow fever, rabies, poliovirus, measles, influenza, adenovirus, and perhaps certain other vaccines. For many years we will need typhoid and BCG vaccines and a large measure of faith in cholera and, in certain limited areas, plague and typhus vaccines. No matter what chemotherapeutic magic may arise, the essential simplicity of prevention by immunization will give it value wherever prevention by other means is less than wholly effective.

Indeed, one may expect that certain immunization practices will be continued indefinitely. To be sure, the eradication approach may eventually solve some current problems. However, even in such a promising instance as smallpox one can reasonably assume that for many years there will remain small isolated groups of people, in areas difficult of access, where smallpox will persist and constitute a recurring threat to the rest of the world.

Clearly, however, we could protect against many additional diseases by immunization if adequate methods were available, especially for those infections for which no convenient, practical alternative means of control is in sight. Yet the problems are multiple. Many unsolved difficulties in disease control revolve around what appear to be basic deficiencies in the antigenic response to the disease, and others are complicated by the multiplicity of antigens concerned. Certainly no single line of research promises success, for on the one hand the patterns of immunity in nature differ tremendously from disease to disease, and on the other hand the specific immunizing antigens in various diseases differ greatly in chemical composition, stability, ease of extraction and purification, and, indeed, in antigenicity. Finally, the var-

ious diseases which concern us differ among themselves in their basic antigenic stability. Contrast, for example, mumps, which clearly has not changed much since the days of Hippocrates, with influenza for which the best we can say is that it hasn't changed much during the last 3 years.

Each disease is a problem in itself, and blueprints for progress will be hard to come by even at a high price. Nevertheless, it is worth the price to try to develop these blueprints; for never in the history of human progress has a better and cheaper method of preventing illness been developed than immunization at its best. In this spirit, it appears worthwhile to define the difficulties that might conceivably be solved by immunological methods and principles.

### What Is Needed

To sharpen the focus, one might start with a list of the disease conditions for which progress in immunization is most needed. Such a list might read as follows.

1. A better vaccine against tuberculosis. BCG is a good vaccine but it is not good enough. A more effective and less reactive vaccine would gain wider acceptance and will be urgently needed if, as may well happen in the next few years, drug resistance outruns the capacity to devise new chemotherapeutic agents that are safe, effective, and readily used on a large scale.

2. An effective vaccine against hemolytic streptococcal infections, or at least against the types most responsible for serious sequelae. Chemoprophylaxis of the complications of streptococcal infections represents a great advance; but it is less than satisfactory to be obliged not only to grab the hose, so to speak, after the chimney catches fire, but then to continue sprinkling the chimney regularly for the next 5 years to prevent flareups.

3. Effective combinations or sequences of immunization against the prevailing upper respiratory infections. This will require great patience and ingenuity, for here the immunologist is challenged to develop the necessary basic understanding of the immune response and the factors which enhance or modify its course, so that he can evoke the requisite mosaic of ade-

quate immune responses to the great variety of respiratory disease agents involved.

4. A durable yet rapidly adaptable system for vaccination against influenza. The problems here are different, notably because of the race against time that ensues when a new strain appears. But we must assume that technical advances can be developed which will surmount such obstacles. I believe that when the next major pandemic occurs we should be able to immunize all except those who are overtaken by the virus within the first few weeks of its emergence.

5. A vaccine or vaccines against the major diarrheas and dysenteries. These infections are as complex as those of the acute respiratory diseases, and equally important. Ultimately, they will be solved by sanitary engineering techniques, but it will be a long time before the people in the areas most affected by these diseases can afford to bring them under control by these methods.

6. An improved vaccine against cholera, needed now for the same reasons.

7. A vaccine against scrub typhus. Area control and chemoprophylaxis may not be adequate for protection of persons pioneering in the development of scrub-infested regions; although immunization in this instance is an especially formidable task, there are potential immunological approaches which have not yet been tried.

8. Better vaccines against several of the more serious arthropod-borne viruses, such as Japanese encephalitis, Russian spring-summer encephalitis, and Kyasanur Forest disease. Development of such vaccines may in turn open the way for the control of the denguelike diseases, and analogous conditions for which control of arthropods will not always be feasible.

9. A vaccine against trachoma. The need is obvious; the problem is difficult; but as I have said, the easy problems have already been solved.

10. A vaccine against the more serious or persistent staphylococcal infections. With these more than with any other infections, the cozy glow of comfort created by the advent of the antibiotics has died out, and the ensuing chill of reality has sent many investigators back to basic immunological studies.

11. A procedure for immunization against hepatitis, granting, of course, the prior assumption of success in isolating the causative agent or agents.

12. Vaccines for control of the so-called minor exanthems, such as varicella and rubella, which, minor though they have long appeared, nevertheless have occasional tragic consequences.

13. We cannot afford to forget the need for seeking effective means of immunization against the major parasitic diseases, trypanosomiasis, schistosomiasis, and malaria. Eventually, all may be subject to area control, but this result is by no means certain; and recent setbacks in the control mechanisms for malaria justify a reexamination of the supposedly insuperable task of immunological protection against this disease.

14. In certain parts of the world, brucellosis will not be eliminated by sanitary measures for many years, and the presently available vaccines are less effective and more reactive than could be desired.

15. Immunization against some zoonoses that I have not mentioned will be important in certain regions of the world, but far more necessary are really effective vaccines against the epizootic diseases that seriously threaten the food supply of major areas of the world: rinderpest, anthrax, African horse sickness, hog cholera, fowl cholera, and others.

16. Control of the allergies has for years been handled as a variant of the principle of immunization, yet this problem is far from solved. Again, further progress in fundamental immunology, already well underway, needs to be sustained in order to reach the goals that now begin to appear attainable.

17. Perhaps equally urgent is the need to develop means of controlling or mitigating so-called delayed or "bacterial" allergy, an aspect of the immune response which is not merely responsible for many reactions to immunization but also appears to play a major role as a cause of persisting symptoms or complications in many chronic infections.

18. Finally, there is growing reason to believe that immunological means may be developed for the control of some, though perhaps by no means all, varieties of cancer and other malignancies.

nant diseases. This prospect alone will suffice to mobilize the greatest talents in immunology, and it is certain that more than one basic approach will have to be explored.

Some will regard this list as inordinately optimistic; others may consider it incomplete. However, it is offered primarily as a basis for discussion and review and as an incentive to new and uninhibited intellectual and scientific adventure. We cannot afford to be bound by the conviction that we know all about the immunological approaches to any of these diseases and conditions, and we may be sure that even less familiar questions will arise in the future.

### **Additional Considerations**

Nor can we sum up the problems of immunization simply with a hopeful list of diseases to be conquered. There are many more general questions to be solved. For example, what will be the role of adjuvants in immunization? The modified Freund adjuvant has been used in perhaps 80,000 to 90,000 inoculations in man. Yet we have relatively little knowledge of its long-term effects. These effects are probably few and may well be insignificant, but we cannot be content to guess the answers to such questions. In any case, the development of an effective and practical adjuvant system demands top priority if multiple immunizations are to be carried out effectively on a large and long-term scale.

Equally needed is clarification of the fundamental stages in the process of inducing an immune response. The development of such knowledge may, at best, show the way to major changes in the entire sequence of immunization procedures; it should at least bring some order out of the present empirical chaos of immunization schedules in which the dose, the interval between injections, the number of injections, and the timing of (or even the need for) booster doses are as varied as the people who write or speak on this subject. Also, we need to find ways to accelerate the primary immune response. An adequate technique for inducing rapid immunization against tetanus, for example, might conceivably do away with the present wasteful and sometimes harmful procedure of prophylactic tetanus antitoxin inoculation.

Studies in the institute of laboratories are being directed to several of these needs, and a number of my fellow immunologists are engaged in basic studies that may yield the necessary breakthroughs in these principles of immunization. But sufficient talent has not yet been enlisted in this task, and those engaged in it must be given every opportunity to develop the knowledge and skills of those who may choose to enter the field. The solution of the problems I have described has far more than theoretical importance; the establishment of simplified, effective immunization schedules may in itself mean the difference between success and failure in applying immunization in developing countries where health departments are understaffed and the populations cannot be reached for the multiple injections customary in the Western World.

Because only the difficult problems remain, there is now a greater need than ever before to support research and to encourage research workers in fundamental microbiology and immunology. Immunology is still far from an exact science, but it is capable of providing some fairly precise information. When we understand more, for example, about the apparent poverty of the immune mechanism in tuberculosis or malaria, more about the genetics of influenzal strain variations, and more about the role of microbial allergy in trachoma, we will then be in a position to undertake control of these diseases more rationally and will be less dependent on luck, serendipity, and a level of patience that is sometimes hard to sustain.

The solution of immunological problems encompasses a variety of scientific disciplines. We are indebted largely to biochemistry and biophysics for the relatively pure toxoids currently available, for the quality and stability of most of the gamma globulin in use, and for the potency and freedom from extraneous substances of the purified poliovirus vaccine recently developed. But no immunization procedures yet developed have equaled those based on the virological luck and skill which led to the establishment of safe, attenuated vaccine strains such as the 17D strain of yellow fever virus. Such attenuated live vaccines generally establish lasting immunity by producing a mild form of the infection itself.

Nevertheless, for some diseases the major breakthrough will come through immunochemical and immunophysical separation, purification, analysis, and eventually even synthesis of the specific substances which initiate the immune response. Others may be met by unraveling the specialized cellular pathways to immunity which appear to be of major importance in many subacute and chronic diseases. Along other lines of investigation we might find, in serum hepatitis, for example, that the virus circulates largely in the raw nucleic acid form. Will it be possible, in such instances, to prevent the disease by immunizing against the nucleic acid core?

Still other mechanisms important to specific immunity are yet to be discovered. We think only in terms of what we know, and inevitably new concepts and discoveries will arise in the future, as new and unexpected as vaccinia virus and diphtheria toxoid were in their day.

There is more to immunity than specific immunity. Many species or strain differences in susceptibility to specific infectious agents fascinate and baffle us. These problems may gradually be solved as knowledge of the precise biochemical processes of infection becomes clarified through the development of experimental studies capable of testing specific and interpretable postulates. In addition, research into nonspecific resistance of the individual host to its own natural parasites is still in the embryonic stage. The hopes engendered a few years ago by the late Dr. Louis Pillemer's brilliant studies on properdin have not been wholly sustained, but they represent an area of research which will be rekindled again, since there is extensive evidence, accumulated over many years, that there are factors in animal serums responsible for significant resistance in its broadest rather than in its conventional narrow sense. The discovery by Isaacs and his colleagues of "interferon" is an exciting example of the unpredictable ways in which this whole area of research may advance at any time.

### **Consequences of Immunization**

However, we rarely get something for nothing, and we cannot ignore the different set of problems which may be engendered by multiple,

repeated immunizations or by other aspects of this process, which is based upon the rather violent procedure of introducing foreign substances into the body. The problem of delayed-type bacterial allergy has been mentioned; there is growing evidence that cumulative sensitization even to tetanus toxoid occurs, and some immunizations are definitely associated with a progressively increasing hyper-reactivity on re-injection. This phenomenon may mount in the future; I believe our only assurance, once again, will be in research on the basic mechanisms underlying immunization and sensitization. These two phenomena may or may not go hand in hand, but we must find out to what extent they are interdependent. A positive tuberculin test appears to be an inescapable consequence of tuberculous infection, but a positive Moloney test is not an inevitable accompaniment to diphtheria immunity. Observations such as these may serve as the directional signals to useful pathways of research.

Other consequences of immunization may be more serious than the reactions I have just mentioned. Aside from the specialized difficulties raised by special techniques—for example, the questions of possible sensitization to kidney tissue from use of monkey kidney tissue culture vaccines or the possibility of inoculating tumor-inducing chromosomal material along with antigens grown in primate tissue—other, more general problems may conceivably follow the injection of foreign substances into man. There is reasonable evidence that certain auto-immune responses may result from the conjugation of "foreign" antigens with host antigens, to cite one example, and we are again reminded that we know too little about the sequence of events that follows the injection of heterologous antigens. The definition of "heterologous" becomes more and more difficult with the recent succession of discoveries suggesting forcefully that each human being may share the complex antigenic mosaic pattern of his tissues with only a few other men on earth.

None of these thoughts need deter the development and application of immunization practices, but they point up once again the paramount importance of fostering, at an equal pace, the support of basic research in immunology and hypersensitivity.

One cannot deal with immunization without considering its obverse, immunological tolerance. Understanding of one underpins understanding of the other. With a better understanding of immunological tolerance and how it is induced or controlled, a host of preventive and therapeutic approaches to surgical, radiological, oncologic, and infectious disease problems will be open to solution.

### Other Needs

Of certain other aspects of the future of immunization there is no need to speculate; the facts are clear. We must now be prepared to accept no half-truths in immunization. We must correctly determine the value for man of the agents now in use and those to be provided in the future, through controlled field trials which yield statistically significant and biologically acceptable data. For too many years we have been content to base acceptance of immunization procedures on relatively raw data in man or on superbly precise studies in mice, or sometimes on nothing much more than wishful thinking. Let us take as a standard the well-known critical evaluations, by controlled field trials, of pertussis, influenza, tuberculosis, and poliomyelitis vaccines, and, on a smaller scale, those of adenovirus, typhoid, and measles vaccines. May the number of vaccines legitimized in this fashion steadily increase.

Vaccination presents sociologic as well as scientific problems. It will do little for the future of immunization to prepare excellent vaccines, test them to a fare-thee-well for safety and efficacy, and then not insure that they are adequately used. We become steadily more impatient as we see science, in this instance as in so many others, outrunning society. I am deeply convinced that a paramount problem in immunization in the future, and one for which we must all share responsibility, is to get vaccines into the people who need them. In a country as civilized as the United States it is shocking to find that about 20 percent of the

youth 15–19 years old and about 40 percent of the young adults 20–29 years old have never had a single injection of poliovirus vaccine. Immunization programs in the developing countries will present similar challenges. They will require not only basic research on the patterns of effective immunization but skilled planning and courageous action to carry through the indicated procedures on an effective scale, and thus to reach the population groups most in need of protection. However, the developing countries may have one real advantage: they can learn from our mistakes.

### Summary

I believe it is fair to say that immunization, while not exactly in its infancy, is scarcely beyond early childhood; that advances in immunization must depend upon vigorous development of knowledge in basic immunology; that, as in other scientific disciplines, major breakthroughs are expected to occur, and that they will, in all probability, occur in unexpected, unforeseen ways. Moreover, these breakthroughs will unquestionably be applicable not only to infectious disease and to allergy in the conventional sense but also to isoallergic disease, tumors, radiological injury, surgical problems, congenital diseases, certain degenerative diseases, and perhaps to other categories, such as geriatric diseases.

Finally, scientific philosophy and intellectual humility must always keep us prepared to see the adverse as well as the advantageous consequences of our actions. Nevertheless, immunization still represents, in principle, the most fortunate discovery ever made in the advancement of human life and health, and its continued fulfillment will proceed in proportion to the brains, talent, and imagination that are devoted to its future.

### REFERENCE

- (1) Burnet, M.: The mechanism of immunity. *Scient. Am.* 204: 58–67, January 1961.